REMARKS

1-Requirement for Restriction

The examiner required restriction to one of several groups of targets recited in the claims under 35 USC 1.121. The applicant has selected the receptor targets, as described above.

2- Amendment

THE CLAIMS

Claims 1-91 are pending in this application, and no claims have been amended. Consideration and allowance of these claims is requested.

THE SPECIFICATION

The applicant submitted with the Amendment of September 28, 2001, marked-up and clean copies of the amended specification pages. Further copies are enclosed herewith for the examiner's convenience. The amendments to the specification are fully supported by the specification, as filed and by the original claims. No objectionable new matter is believed to have been introduced by this amendment.

THE FEE

The Assistant Commissioner, however, is hereby authorized to charge to PTO Account No. **50-1728**, the amount of $200.- for an extension fee of two months, which is herewith being requested. In view of the above amendments and remarks, this application is believed to be in condition for examination and allowance. Early notice to that effect is hereby solicited.

Respectfully submitted.
EPIGENESIS PHARMACEUTICALS, INC.

January 4, 2002

Date

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I hereby certify that this correspondence is being deposited at the United States Postal Service, First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington D C 20231, on January 4, 2002, by Rashida Haji.

R. Haji
SIGNATURE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification

Section beginning from page 296, line 56, to page 298, line 60, has been amended as follows (from next page):

GGATATAGGT TTCCAATTAA GTACATGGTC AAGTATTAAC AGCACAAGTG GTAGGTTAAC ATTAGAATAG
GAATTGGTGT TGGGGGGGGG GTTTGCAAGA ATATTTTATT TTAATTTTTT GGATGAAATT TTTATCTATT
ATATATTAAA CATTCTTGCT GCTGCGCTGC AAAGCCATAG CAGATTTGAG GCGCTGTTGA GGACTGAATT
ACTCTCCAAG TTGAGAGATG TCTTTGGGTT AAATTAAAAG CCCTACCTAA AACTGAGGTG GGGATGGGGA
GAGCCTTTGC CTCCACCATT CCCACCCACC CTCCCCTTAA ACCCTCTGCC TTTGAAAGTA GATCATGTTC
ACTGCAATGC TGGACACTAC AGGTATCTGT CCCTGGGCCA GCAGGGACCT CTGAAGCCTT CTTTGTGGCC
TTTTTTTTTT TTCATCCTGT GGTTTTTCTA ATGGACTTTC AGGAATTTTG TAATCTCATA ACTTTCCAAG
CTCCACCACT TCCTAAATCT TAAGAACTTT AATTGACAGT TTCAATTGAA GGTGCTGTTT GTAGACTTAA
CACCCAGTGA AAGCCCAGCC ATCATGACAA ATCCTTGAAT GTTCTCTTAA GAAAATGATG CTGGTCATCG
CAGCTTCAGC ATCTCCTGTT TTTTGATGCT TGGCTCCCTC TGCTGATCTC AGTTTCCTGG CTTTTCCTCC
CTCAGCCCCT TCTCACCCCT TTGCTGTCCT GTGTAGTGAT TTGGTGAGAA ATCGTTGCTG CACCCTTCCC
CCAGCACCAT TTATGAGTCT CAAGTTTTAT TATTGCAATA AAAGTGCTTT ATGCCCGAAT TC-3' **(FRAG.NO:_) (SEQ. ID NO:2497)**

5' GCCGCCGCCA TGGGAGTGCA GGTGGAAACC ATCTCCCCAG GAGACGGGCG CACCTTCCCC AAGCGCGGCC
AGACCTGCGT GGTGCACTAC ACCGGGATGC TTGAAGATGG AAAGAAATTT GATTCCTCCC GGGACAGAAA
CAAGCCCTTT AAGTTTATGC TAGGCAAGCA GGAGGTGATC CGAGGCTGGG AAGAAGGGGT TGCCCAGATG
AGTGTGGGTC AGAGAGCCAA ACTGACTATA TCTCCAGATT ATGCCTATGG TGCCACTGGG CACCCAGGCA
TCATCCCACC ACATGCCACT CTCGTCTTCG ATGTGGAGCT TCTAAAACTG GAATGACAGG AATGGCCTCC
TCCCTTAGCT CCCTGTTCTT GGATCTGCCR TGGAGGGATC TGGTGCCTCC AGACATGTGC ACATGARTCC
ATATGGAGCT TTTCCTGATG TTCCACTCCA CTTTGTATAG ACATCTGCCC TGACTGAATG TGTTCTGTCA
CTCAGCTTTG CTTCCGACAC CTCTGTTTCC TCTTCCCCTT TCTCCTCGTA TGTGTGTTTA CCTAAACTAT
ATGCCATAAA CCTCAAGTTA TTCA-3' **(FRAG. NO:_) (SEQ. ID NO:2498)**

wherein B is adenosine, or, more preferably, replaces adenosine and is an "equivame\\lent" or a "universal" base, and adenosine A_{2a} receptor agonist or only minimally antagonist, an adenosine A_{2b} receptor antagonist, an adenosine A_3 receptor antagonist, or an adenosine A_1 receptor antagonist. Similarly, adenosine (A) may always be replaced by an "alternative", "equivalent" and/or "universal" base having a small fraction, preferably less than 0.3 of the activity of adenosine at the adenosine receptor(s), as described above.

In one preferred embodiment, the links between neighboring mononucleotides are phosphodiester links. In another preferred, at least one mononucleotide phosphodiester residue of the anti-sense oligonucleotide(s) is substituted by a methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, 2'-O-methyl, methylene(methyimino), methyleneoxy (methylimino), phosphoramidate residues, and combinations thereof. The oligos having one or more phosphodiester residues substituted by one or more of the other residues are generally longer lasting, given that these residues are more resistant to hydrolysis than the phosphodiester residue. In some cases up to about 10%, about 30%, about 50%, about 75%, and even all phosphodiester residues may be substituted (100%). Typically, the multiple target anti-sense oligonucleotide (oligo) of the invention comprises at least about 7 mononucleotides, in some instances up to 60 and more mononucleotides, preferably about 10 to about 36, and more preferably about 12 to about 21 mononucleotides. However, other lengths are also suitable depending on the length of the target macromolecule. Examples of the MTA oligos of the invention are provided in Table 3 below, which includes ninety-four sequences (SEQ ID NOS.: 2316 through 2410).

Table 3: MTA Oligos, Location Targeted & Target

MTA Oligo	SEQ. ID No.	Location	Compound Targeted	Target
HUMNFKBP65A AS				
CCC GGC CCC GCC TCG TGC C	3019	5'=1	EPI 2192	
CGT CCB TGC CGC GGG CCC	3020	5'=28(AUG)	EPI 2193	
GCC CCG CTG CTT GGG CTG CTC TGC CGG G	3021	5'=65	EPI 2194	
TCT GTG CTC CTC TCG CCT GGG	3022	5'=137	EPI 2195	
TGG TGG GGT GGG TCT TGG TGG	3023	5'=159	EPI 2196	
CTG TCC CTG GTC CTG TG	3024	5'=196	EPI 2197	
GGT CCC GCT TCT TC	3025	5'=362	EPI 2198	
GGG GTT GTT GTT GGT CTG G	3026	5'=401	EPI 2199	
TGT CCT CTT TCT GC	3027 [3026]	5'=656	EPI 2200	
GCC TCG GGC CTC CC	3028 [3027]	5'=697	EPI 2201	
GGC TGG GGT CTG CGT	3029 [3028]	5'=769	EPI 2202	

GGC CGG GGG TCG GTG GGT CCG CTG	3030[3029]	5'=953	EPI 2203	
GGG CTG GGG TGC TGG CTT GGG G	3031[3030]	5'=1022	EPI 2204	
GGG GCT GGG GCC TGG GCC	3032[3031]	5'=1208	EPI 2205	
GCC TGG GTG GGC TTG GGG GC	3033[3032]	5'=1272	EPI 2206	
GCT GGG TCT GTG CTG TTG CC	3034[3033]	5'=1362	EPI 2207	
GTT GTG TGG GGG GCC	3035[3034]	5'= 1451	EPI 2208	
GCT GGG TCG GGG GGC CTC TGG GCT GTC	3036[3035]	5'=1511	EPI 2209	
GCC CCG GGG CCC CC	3037[3036]	5'=1550	EPI 2210	
TGG CTC CCC CCT CC	3038[3037]	5'=1772	EPI 2211	
GCT CCC CCC TTT CC	3039[3038]	5'=1863	EPI 2212	
CGG ACG AAG ACA GAG A	3040[3039]	5'=1979	EPI 2213	
GGC TTT GTG GGC TC	3041[3040]	5'=2011	EPI 2214	
GCC TGC TCT CCC CC	3042[3041]	5'=2312	EPI 2215	
CCC GGC CCC GCC BCG BBC C	3043[3042]	intron	EPI 2192-01A	HSU50136C4Synth
CCC GGC CCC GCC BCG	3044[3043]	intron	EPI 2192-01B	
CCC GGC CCC GCC BCG BBC C	3045[3044]	5'untr	EPI 2192-02A	HUMLIPOX5LO
CCC GGC CCC GCC BCG	3046[3045]	5'untr	EPI 2192-02B	
CCC GBC CCC GCC TCB BG	3047[3046]	trans	EPI 2192-03A	HSNFKBS Subunit
CCC GBC CCC GCC TC	3048[3047]	trans	EPI 2192-03B	
CCG GCC CCG CCT C	3049[3048]	5'untr	EPI 2192-04	TGFβR1
CCC GBB CCC GCB TBG TGC C	3050[3049]	5'trans	EPI 2192-05A	HSU58198Il enhan
CCC GCB TBG TGC C	3051[3050]	5'untr	EPI 2192-05B	
CCC GGB CCC BCC BBG TGC C	3052[3051]	3'trans	EPI 2192-06	HSVECAD
CBG BBC CCG CCT CGT GCC	3053[3052]	intron	EPI 2192-07A	NFKB2
C CCG CCT CGT GCC	3054[3053]	intron	EPI 2192-07B	NFKB2
CCG GCB CCG CCT CBT GCC	3055[3054]	5'trans	EPI 2192-08	Carboxypep
CCG GCC CCG CCB CBT GCC	3056[3055]	3'trans	EPI 2192-09	HumADRA2Cα2AdrKid
CCC GBC CCC GBC TCG	3057[3056]	5'untrs	EPI 2192-10	HUMFK506B
CCC GGC CBC GBC TCG	3058[3057]	5'untrs	EPI 2192-11	HSNBARKS1βAdrKin
CCC GGC CCB GCC TBG	3059[3058]	5'UTR	EPI 2192-12	HSNFXN1(NFKB1)
CCC GGC BCB GBC TCG TBC C	3060[3059]	3'UTR	EPI 2192-13	HSILF(transcrp. Factor ILF)
CCC GGC CCC GCC BCG	3061[3060]		EPI-2192-14	NFKB/C4Syn/5-LO/ TGFBrec1 MTA
CCC GGC CCC GCC BCG	3062[3061]		EPI-2192-15	NFKB/C4Syn/5-LOMTA
TCC BTG CCG CGG GC	3063[3062]	3' trans	EPI-2193-01	METOncogene
TCC BTG CCB CGG GCC	3064[3063]	3' trans	EPI-2193-02	HSFGR2(IG)
TCC BTG CCB CGG GCC	3065[3064]	mid cod	EPI-2193-03	5-LO
TCC BTG CCB CBG GCC	3066[3065]	mid cod	EPI-2193-04	HUMTK14
GTC CBT GBC GCG G	3067[3066]	3'trans	EPI-2193-05	HUMTNFR
TC CBT GBC GCG GG	3068[3067]	AUG		Probl.HUMPTCH cardiacK+channel
TCT GBG CTC CTC TBB CCT GGG	3069[3068]	intr	EPI-2195-01	humCSPAcytotox. Ser.Protease
CTG TGC BCC TBB CBC CTG GG	3070[3069]	intr	EPI-2195-02	HSINOSX08induc.NOS
TGT GBT CCB CTB GBC TGG G	3071[3070]		EPI-2195-03	HUMACHRM2musc.m2 acetylch.rec.
TCT GTB CTC BBC TCB CCT G	3072[3071]		EPI-2195-04	s86371s1 Neurokinin3Recept
TGC TCC TCB CBB CTG GG inflam.factor	3073[3072]	EPI-2195-05	HUMMIP1 Amacro	

Table 3: MTA Oligos, Location Targeted & Target (Cont'd)

MTA Oligo	SEQ. ID No.	Location	Compound Targeted	Target
CTC CTC TBG CCT GG	3074 [3073]		EPI-2195-06	HSNBARKS4 β-Adr Rec Kinase
GTG CTC CBB TCB BCT GGG	3075 [3074]		EPI-2195-07	HSTNFR2SO6TNF R2
GTG CBC CBB TCB CCT GGG	3076 [3075]		EPI-2195-08	humfkbp fk506 binding prot.
TCT GTG CBC CTC TBG BCT	3077 [3076]	exon	EPI-2195-09	HSNBARKS1β-Adr. Recept.Kinase
CTG TBB TCC TBB CBC CTG G	3078 [3077]	intron	EPI-2195-10	HUMIL8
TGT GCT BBT CBC BCB TGG G	3079 [3078]		EPI-2195-11	HSU50157 PDE4
GTG CBC CBC TCB CCT G	3080 [3079]	intron/exon	EPI-2195-12	IL-2 R
CTG TGC BCC TCT C	3081 [3080]	3'UTR	EPI-2203-05	IL-6 R HSIL6R
CBG TGC BCC BCT CBC CTG	3082 [3081]	intr/ex	EPI-2203-06A	HSIL2rG6
G TGC BCC BCT CBC CTG	3083 [3082]	intr/ex	EPI-2203-06B	HSIL2rG6
CBC CTC TCB CCT GGG	3084 [3083]	coding	EPI-2203-07A	HUMIL71
C CTC TCB CCT GGG	3085 [3084]	coding	EPI-2203-07B	IL-7 HUMIL71
GCT CCB CTC GCC T	3086 [3085]	coding	EPI-2203-08	IL-6 R HSI6REC
TGC TCC TCB CGC C	3087 [3086]	intron PDGF A	EPI-2303-09	Chain HUMPDGFAB
GTT GTT GBT CTG G	3088 [3087]	3'utr	EPI-2199-01	GATA-4Transcrip. Factor for IL-5
GGT TGB BBT TGG TCT TGG	3089 [3088]	Coding	EPI-2199-02	TNFα HUMTNFA
GGT TGT TGB TGB TCT G	3090 [3089]	Far 5'UTR	EPI-2199-03	HSSUBP1G(Sub Pr)
GGG TTB BBG TTG BTC TGG	3091 [3090]	Coding	EPI-2199-04	NeutrophilAdh. R HUMNARIA
GGG TTB BBG TTG BTC TGG	3092 [3091]	HSHM2	EPI-2199-05	m2 Muscarinic R
TTG TTG TBG BTC TGG	3093 [3092]	HUML1CAM	EPI-2199-06	L1 LeukAadhProt
GGG TBG BBG BGT CCG CTG	3094 [3093]	coding	EPI-2203-01	HUMGATA2A
GGG TCB GBG GBT CBG CTG	3095 [3094]	S71424S2	EPI-2203-02	IGE eps
GGG TBG GTG GGT C	3096 [3095]	coding	EPI-2203-03	HSGCSFR2
GGG TCG GBG GGT CBG C	3097 [3096]	HUMITGF	EPI-2203-04	TGFβ3
GGG TGG GCT T	3098 [3097]	HUMNK65PRO	EPI-2206-01	NFKB/NK & TCell Activating Prot
GGG TGG GCT TGG G	3099 [3098]	HUMPEREEB	EPI 2206-02	NFKB/Prostagl. EP3 Rec
CCTGGGTGGGBBTGGG	3100 [3099]		EPI 2206-03	HSNF2B/GCSF NFKB/GranuLocCSF/ Transcr.FactorNF2B
CCTGGBTGGGCBTGGG	3101 [3100]		EPI-2206-04	HUMLAP/NFKB Leuk.Adhes.Prot
GCCTGBGTGBBCTTGGG	3102 [3101]		EPI2206-05	NFKB/Endothel N2 S63833
CCCAVGVCCVCCCAGGC	3103 [3102]		EPI 2206-06	NFKBAS13/B Lymph SerThrProt.Kinase
AGCCCACCCAGGC	3104 [3103]		EPI2206-07	NFKBAS13/GCSF1 HSGCSFR1Rec
BCCTGGGTGGGCTB	3105 [3104]		EPI2206-08	NFKBAS13/GCSF1/ NK7TCELLACT.Prot
GGTGGGCTTGGG	3106 [3105]		EPI 2206-09	NFKBAS13/ HSTGFB1 TGFB
CCBBGGTGGGCTTGGG	3107 [3106]		EPI 2206-10	NFKBAS13/ HSTGFB1 TGFB1
CTGGGTGGGBBTGGG	3108 [3107]		EPI 2206-11	NFKBAS13/ HSGCSFR1 GCSFR1
CCBGGGTGGGCTTGG	3109 [3108]		EPI 2206-12	NFKBAS13/HUMCD30A LymphActAntigCoding
GGGTGGGCTTGG	3110 [3109]		EPI-2206-12B	NFKBAS13/HUMCD30A
CCTGBGTGBGCBTGGG	3111 [3110]		EPI 2206-13	NFKBAS13/HUMCAM1V Vasc.Endoth.Cell Adh.Molec

B: Universal Base

The MTA oligos of Table 3 are suitable for use with two or more of the targets listed in Table 4 below.

CLEAN VERSION

In the specification

Please enter the following pages 296 through 298 for the substitution of the previous original pages (starting from next page):